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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/723,174	11/26/2003	Katrin Kneipp	M0925.70114US01	5755
7590 Timothy J. Oyer, Ph.D. Wolf, Greenfield & Sacks, P.C. 600 Atlantic Avenue Boston, MA 02210			EXAMINER HINES, JANA A	
			ART UNIT 1645	PAPER NUMBER
SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE		
3 MONTHS	12/29/2006	PAPER		

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/723,174	KNEIPP ET AL.	
	Examiner	Art Unit	
	Ja-Na Hines	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 17 October 2006.

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) See Continuation Sheet is/are pending in the application.
4a) Of the above claim(s) See Continuation Sheet is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 188-195 and 198-202 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) Notice of References Cited (PTO-892)
2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date .
4) Interview Summary (PTO-413)
Paper No(s)/Mail Date. .
5) Notice of Informal Patent Application
6) Other: .

Continuation of Disposition of Claims: Claims pending in the application are 1-17,19, 23-37,39,43-58,60,64-72, 74, 78-85,87,91-117,122, 125-126, 128, 130, 132-135,138,139,146,147,153,155-157,159-162,164,172,179,180,182,183 and 187-202.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 1-17, 19, 23-37,39,43-58,60,64-72, 74, 78-85,87,91-117,122, 125-126, 128, 130, 132-135,138,139,146,147,153,155-157,159-162,164,172,179,180,182,183, 187 and 196-197.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 17, 2006 has been entered.

Amendment Entry

2. The amendment filed August 11, 2006 has been entered. Claims 190-194 and have been amended. Claim 202 has been newly added. Claims 1-17, 19, 23-37,39,43-58, 60, 64-72, 74, 78-85,87,91-117,122, 125-126, 128, 130, 132-135, 138, 139, 146, 147,153,155-157,159-162,164,172,179,180,182,183, 187 and 196-197 have been withdrawn from consideration. Claims 18, 20-22, 38, 59, 61-63, 73, 75-77, 86, 88-90, 118-121, 123-124, 127, 129, 131, 136-137, 140-145, 148-152, 154, 158, 163, 165-171, 173-178, 181, 184-186 have been cancelled. Claims 188-195 and 198-202 are under consideration in this office action.

Priority

3. Applicants' claim for domestic priority under 35 U.S.C. 119(e) is denied. Applicants assert that US Provisional application 60/076,310 relates to methods for

detection of analytes, including sequencing DNA or RNA. Applicants' also urge that the application teaches DNA/RNA fragments can be cleaved with enzymes, SERS, and fragmenting techniques at page 14. However, the passage to which applicants refer begins on page 13, line 29. The provisional specification states that all the techniques, including the cleavage technique is associated with technique for obtaining a unique piece of spectral information, such as unique portion of a spectrum defining a single line attributed to a DNA/RNA fragment. The provisional specification does not recite a method for determining a sequence as recited by the instant claims.

At best, there is support for a method for sequencing DNA or RNA fragments, comprising: allowing a plurality of DNA or RNA fragments to become surface-adsorbed; exposing each base to electromagnetic radiation to cause surface-enhanced emission; and obtaining unique surface-enhanced spectroscopic information attributed to each base, see page 4, line 27. Thus the provisional application's disclosed method has different steps which are unsupported. Thus, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 188-195 and 199-202 of this application.

Therefore, the provisional application 60/076,310, fails to teach the instantly claimed method. There is no teaching of a method for determining a sequence of at least a portion of a DNA or RNA strand comprising the instantly recited steps. Thus, applicants' arguments are not persuasive and priority cannot be granted to 60/076,310, since what is now claimed, have not been previously recited in that application.

Withdrawal of Rejections

3. The rejection of claims 190-194 under 35 U.S.C. 112, second paragraph, has been withdrawn in view of applicants' amendments and arguments.

Response to Arguments

4. Applicant's arguments filed August 11, 2006 have been fully considered but they are not persuasive.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. The rejection of claims 188-195 and 198-202 are rejected under 35 U.S.C. 102(b) as being anticipated by Vo-Dinh (US Patent 5,306,403) is maintained for reasons already of record. The rejection was on the grounds that Vo-Dinh teach a method for determining a sequence of at least a portion of a DNA or an RNA strands comprising: a) fragmenting one or more bases from a DNA or an RNA strand using a nuclease to form a plurality of fragments each fragment comprising at least one base; b) sequentially identifying each of the one or more fragments by Raman spectroscopy; and c) determining the sequence of at least a portion of the DNA or RNA strand based on

the sequential identification of each of the one or more fragments, just as required by the instant claims.

Applicants' assert that Vo-Dinh does not actually disclose sequences a DNA or RNA strand. However Vo-Dinh discloses inventions to provide a Raman-based DNA sequencing method and apparatus that is capable of accurate, fast and efficient DNA sequencing. Another object of the present invention is to provide a Raman-based DNA sequencing method and apparatus that is capable of providing an understanding of the human genome structure in general. Another object of the present invention is to provide a Raman-based DNA sequencing method and apparatus that provides improved DNA sequence detection and is useful for analyzing new DNA labels, nucleotides or oligonucleotides that cannot be monitored by other spectroscopic methods, see col. 3, lines 10-25. Therefore applicants' assertion is no persuasive.

Applicants urge that the cleavage taught by Vo-Dinh is drawn to cleavage by the restriction endonuclease at specific recognition sequences of four to eight base pairs. However, the instant claims require fragmenting one or more bases from a DNA or an RNA strand using a nuclease to form a plurality of fragments each fragment comprising at least one base. Vo-Dinh teach fragmenting or cleavage of fragments or one or more bases using restriction endonucleases; thus Vo-Dinh teach the limitations of the claim. The fact that Vo-Dinh uses known strands, is not persuasive, because there is no limitation on the strand being known or unknown. Furthermore, the claim encompasses the identification of a known sequence within a sample based on a probe that was previously prepared. Therefore, applicants' argument is not persuasive.

Applicants' assert that Vo-Dinh does not disclose or suggest determining the sequence based on sequence identification of each one or more fragments by Raman Spectroscopy. Applicants again argue that because the restriction enzymes cleave the DNA into fragments defined by the restriction site, Vo-Dinh does not teach the instant invention. However, as previously stated, the only recited limitation on fragmenting is that one or more bases be fragmented using a nuclease. Vo-Dinh meets the limitation, by fragmenting four to eight bases, just as required by the claims.

Applicants argue that Raman spectroscopy is not used by Vo-Dinh. However Vo-Dinh is replete with the use of Raman spectroscopy. Vo-Dinh teaches the attachment of a surface enhanced Raman scattering (SERS) label on the DNA fragments for sequencing. The sequencer apparatus allows for sequential identification. In the embodiments of FIGS. 3 and 4, the SERS labels were attached to the DNA fragments or oligonucleotides and, after separation of DNA fragments, the SERS labels can be detected when they are still bound to the DNA fragments. A variation of this technique would involve detecting the SERS labels after the SERS labels are selectively detached from the DNA fragments and transferred onto a SERS substrate. The membrane has a SERS-active material on the surface thereof. A light detector collects scattered light and processes the same into a readable output, such as a trace showing wavelength and SERS intensity. The structure described can be used for automated multiplex sequencing with a moving SERS substrate. Therefore, contrary to applicants' assertions, Vo-Dinh teaches Raman spectroscopy to sequence DNA fragments.

Thus, applicants' arguments are not persuasive and the rejection over Vo-Dinh as teaching a method for determining a sequence of at least a portion of a DNA or an RNA strands, just as instantly claimed, is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

7. The rejection of claims 188-195, 198-199 and 201-202 under 35 U.S.C. 103(a) as being unpatentable over Dorre et al., in view of Kneipp et al., (Physical Review Letters, Vol. 78(9): 1667-1670 March, 1997) is maintained for reasons already of record. The rejection was on the grounds that it would have been *prima facie* obvious at the time of applicants' invention to modify the method for determining a sequence of at least a portion of a DNA or an RNA as taught by Dorre et al., wherein the modification exchanges fluorescence detection for SERS detection as taught by Kneipp et al., because Kneipp et al., teach that Raman spectroscopy is complementary to fluorescence but offers additional properties.

Applicants' assert that Kneipp et al., is unavailable as a reference because they are entitled to the priority date. However as discussed above, the provisional application 60/076,310, fails to teach the instantly claimed method. It appears that there is no teaching of a method for determining a sequence of at least a portion of a DNA or RNA

strand comprising the instantly recited steps. Thus, applicants' arguments are not persuasive and priority cannot be granted to 60/076,310, since what is now claimed, have not been previously recited in that application.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, to modify the method for determining a sequence as taught by Dorre et al., wherein the modification exchanges fluorescence detection for SERS detection as taught by Kneipp et al., requires no more than routine skill because Kneipp et al., teach that Raman spectroscopy is complementary to fluorescence but offers additional properties. Moreover, one would have a reasonable expectation of success in determining the sequencing method using Raman spectroscopy instead of fluorescence since it provides a high degree of structural information about the molecule; requires shorter time for detection; and avoids photodecomposition. Thus no more than routine skill would have been required to exchange an alternative yet functionally equivalent method of detection when the art teaches the beneficial properties associated with the exchange.

In response to applicant's argument that Dorre et al., teach sequencing using fluorescent techniques and cannot be combined with Kniepp et al.,; it is noted that the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). In this case, the combined teaching clearly that Raman spectroscopy is complementary to fluorescence but offers additional properties such as: 1) SERS's vibrational spectrum provides a high degree of structural information about the molecule; 2) SERS allows for shorter integration times for detecting a molecules or higher rates for counting single molecule; and 3) SERS avoids photodecomposition of the probed molecules because the excitation energy is not in resonance with molecular transitions. Thus applicants' argument is not persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Thus applicants' argument that Dorre et al., do not disclose or suggest substituting Raman spectroscopy for fluorescence microscopy is not persuasive. Kniepp et al., clearly provides motivation for exchanging fluorescence microscopy for Raman spectroscopy. Kniepp et al., teach that methods for selective and rapid detection of

single molecules using excited fluorescence is already known in the art and that Raman spectroscopy is a complementary spectrochemical technique. Therefore applicants' argument is not persuasive and the rejection is maintained.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In this case, only knowledge which was within the level of ordinary skill at the time the claimed invention was made is used; such knowledge is disclosed by Kneipp et al. Thus, it is not hindsight reasoning since the art teaches that it would have been obvious at the time of applicants invention to modify the method for determining a sequence of at least a portion of a DNA or an RNA as taught by Dorre et al., wherein the modification exchanges fluorescence detection for complementary spectral SERS detection as taught by Kneipp et al. Therefore, applicants' arguments are not persuasive and the rejection is maintained.

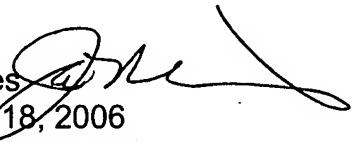
Conclusion

9. No claims allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached on Monday-Thursday and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Jeffery Siew, can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ja-Na Hines 
December 18, 2006